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Carcinogenicity of Airborne Fine Particulate Benzo(a)pyrene: An Appraisal of the Evidence and the Need for Control

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Benzo(a)pyrene (BaP) originating from fossil fuel and other organic combustion processes is largely adsorbed on fine particulate and hence is a widespread atmospheric pollutant. Available emissions and air quality data are based on the total weight of particulate matter without reference to size and give little information on trends and concentrations of fine particulate BaP. Greater reliance on coal, synfuels and diesel fuel for energy production and transportation will significantly increase ambient levels of BaP.

Because of the particulate size, BaP is substantially deposited in the lower lung and readily eluted into surrounding tissue. After elution in the lung, BaP is metabolically activated to its electrophilic, carcinogenic form by a complex enzyme system whose activity is increased by prior exposure to air pollutants, cigarette smoke and certain drugs. The resultant diol epoxide metabolite has been shown to bind covalently with the DNA of the lung. In experimental animals, BaP is a potent initiating carcinogen whose action is enhanced by sulfur dioxide, promoting agents and carrier fine particles. The effect of small, divided doses of BaP has been shown to be greater than that of a single high dose; no threshold has been established. Epidemiological studies show that mixtures containing BaP (such as urban air, industrial emissions and cigarette smoke) are carcinogenic and may interact synergistically. Occupational studies indicate that the action of BaP-containing mixtures is enhanced in the presence of SO_2.

However, quantitative risk assessment for BaP is precluded by problems in extrapolating to the general population from small-scale animal studies; uncertainties in findings of epidemiology; and imprecise exposure data. Existing stationary and mobile source controls preferentially remove coarse particulate matter and are inefficient collectors of fine particulate BaP. In the current absence of health and environmental standards for BaP, there is little incentive to control BaP emissions. BaP meets the criteria for regulation under the Clean Air Act; however, no such BaP standards have yet been proposed.

Introduction

This paper contains a broad review of the literature pertaining to the carcinogenicity of environmental BaP. The discussion ranges from recent research on the mode of action of BaP to the ambient levels of this pollutant and the technologies that may be used to control emissions from major sources. The review is set in the context of present policies that are predicted to substantially increase concentrations of atmospheric BaP.

The purpose of the paper is to summarize some of the major findings since 1972 when the National Academy of Sciences (NAS) published a comprehensive review of BaP in its report entitled

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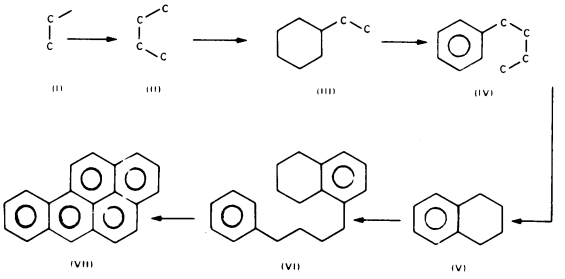
Particulate Polycyclic Organic Matter. During the last eight years, for example, there have been major advances in understanding of the importance of the fine particulate fraction of air pollution with which BaP is largely associated as well as of the molecular processes involved in the carcinogenicity of BaP.

For background reading, the reader is referred to two basic references: Polycyclic Hydrocarbons and Cancer, Vols. 1 and 2 (*1*) and Carcinogenesis, Vols. 1 and 3: Polynuclear Aromatic Hydrocarbons (*2*).

Origin, Physical and Chemical Properties of BaP

Formation and Use as an Index

Benzo(a)pyrene is a polycyclic aromatic hydrocarbon consisting of five aromatic rings. BaP is formed during combustion of any organic material such as fossil fuels. At high temperatures of combustion (greater than 400-500° C) organic fragments or radicals are formed which subsequently combine to form BaP [Eq. (1)] (*3*, *4*). Following release from the combustor flame as a vapor, BaP either condenses onto inorganic particles or coalesces to form particles of pure condensate (*5*). Other carcinogenic polycyclic aromatic hydrocarbons (PAH) are formed in the same process.



(1)

There is reasonably good correlation of various PAH with BaP in the emissions from certain sources; this fact, combined with the availability of analytical methods for BaP, has led to the use of BaP as an indicator for PAH and even for the potential carcinogenicity of air pollution (*6-8*). However, the observation that the correlation between PAH and BaP varies by location (*9*, *10*) as well as the fact that many non-PAH carcinogens are present in air (*11-13*) argue that BaP is a useful indicator for both PAH and carcinogenicity of air only in certain circumstances (*10*, *14*). Therefore, BaP will be treated here as an important atmospheric carcinogen in its own right: it is the quantitatively most important carcinogen in soot arising from fossil fuel burning (*5*, *6*) as well as a major initiating carcinogen in cigarette smoke (*7*), in coal gasification effluent and coke oven emissions (*15*).

Emission Sources

Man-made BaP arises from fuel combustion by mobile sources such as gas and diesel-powered vehicles and stationary sources including heat and power generation, refuse burning, and industrial activities (*4*). EPA estimates that in 1975, 2% of BaP came from mobile sources, 4% from stationary combustion of oil, and 80% from combustion of coal (*16*).

According to the National Academy of Sciences, about 1300 tons of BaP are emitted by stationary sources each year (Table 1).

All of the data in Table 1 are based on very limited information and are therefore of questionable validity. In particular, Guerin (*5*) and Baum (*9*) have pointed out that the data for coal burning power plants may seriously understate actual amounts of BaP released. First the figure of 1.0 ton per year is based on 1960 data and does not take account of probable increases in release of BaP as a result of control measures to meet EPA's nitrogen oxide standard for fossil fuel steam generation plants (*17*). Second, since BaP is released in vapor state, the conventional stack sampling system that does not use an organic vapor adsorbent fails to capture a significant proportion of BaP (*18*). Jones et al. report from two to ten times as much polycyclic organic matter (POM) measured in effluents using an adsorbent sampler compared to that measured by conventional techniques (*5*, *19*). BaP emissions may therefore be an order of magnitude greater than those predicted by traditional methods.

Table 1. BaP emitted by stationary sources.[a]

Source	BaP, tons/yr
Heat and power generation	
Coal (residential furnaces)	420.0
Coal (intermediate units)	10.0
Coal (coal-fired steam power plants)	1.0
Wood	40.0
Oil	2.0
Gas	2.0
Industrial plants	
Petroleum and asphalt	7.0
Coke production	200.0
Refuse burning	600.0
Total	1282.0

[a]Based on NAS data (*4*).

Furthermore, it is important to recognize that because BaP generally takes the form of fine, relatively weightless particulates, even substantial increases in respirable BaP will not be reflected in gross tonnage figures such as in Table 1. (Fine particulates are here defined as those smaller than several micrometers in diameter.)

Three sources in Table 1 are expected to increase atmospheric levels of BaP significantly either as a result of the present national energy program or as an initiative to achieve motor vehicle fuel economy standards. These are stationary combustion of coal and synthetic fuels (synfuels) for production of heat and energy and the increased use of diesel fuel by automobiles.

Coal burning currently produces more BaP than any other stationary source (*4*) and is estimated to produce more than half of man-made nitrogen oxide emissions; and substantial amounts of trace elements and radionuclides (*20, 21*). Depending on the type of coal and combustion efficiency, a coal burning power plant can emit from 19-400,000 $\mu g/10^6$ BTU (*6*); hourly emissions can be as high as 50 mg BaP for a plant rated from 1 to 2 $\times$ 10^6 lb steam/hr (*5*). Wilson et al. (*22*) have reported that 12.9 ng/m^3 of BaP was measured in the stack of a coal burning power plant while 16.2 ng/m^3 and 8.2 ng/m^3 of BaP were found in the plume at distances of 0-5 and 5-10 miles from the plant.

In 1977, President Carter called for a doubling of coal use in power plants by 1985 (*23*). To date, over 100 oil-burning facilities have received proposed orders to convert to coal under the Industrial Power Plant Fuel Use Act (IPPFUA) and the Energy Supply and Environmental Coordination Acts (ESECA), and thirteen final orders have been issued under ESECA (*24*). Last spring, Congress considered legislation requiring an additional 50 power plants to shift to coal use (*25*). As an incentive for conversion, President Carter proposed to give $4 billion to utilities that shift to coal (*26*).

Utilities now burn over 400 million tons of coal to produce about 44% of the nation's electricity. Based on three energy scenarios, the OTA (1979) projects a 70-90% increase in utility coal combustion by 1985, growing to 140-250% by 2000 (*21*). For residential and commercial sources, OTA (1979) predicts a doubling by the year 2000 and as much as a tripling by 1985 in industrial coal (*21*). Both are already very significant sources of BaP (*27*).

Combustion of diesel motor fuels yields widely varying amounts of BaP (from virtually undetectable levels up to 1,687 $\mu g/min$) depending upon factors such as efficiency of operation, level of maintenance, workload, etc. (*28*). For example, Hangebrauck et al. (*29*) reported a significantly higher BaP emissions factor for diesel (690 $\mu g/gal$ fuel) than for gasoline-powered automobiles (170 $\mu g/gal$ fuel) and trucks (460 $\mu g/gal$ fuel). According to EEA (*30*), however, the best estimate of BaP emissions from diesel automobiles is 38 $\mu g/l.$ (or 106 $\mu g/gal$) of diesel fuel burned. In one study, particulate emissions from diesel automobile engines were estimated to contain ten times the amount of BaP found in emissions of gasoline powered cars equipped with catalytic converters (*31*). Another report estimates BaP in exhaust from a light-duty diesel vehicle to be 10-60 times greater than in exhaust from a catalyst controlled light-duty gasoline vehicle (*32*). As with coal emissions, the BaP is found in a mixture of fine particulate sulfate, nitrate, and organic substances, trace metals, along with gaseous sulfur and nitrogen oxides (*33*).

Several American automobile manufacturers in search of greater fuel economy have announced their intention to increase diesel production so that about 25% of new automobiles sold in the U.S. by 1990 will be diesels (*34*). This projection is troubling in light of existing evidence of the ability of extracts of diesel emissions to cause mutations and DNA damage in tests widely considered to be indicators of human carcinogenicity (*35, 36*).

The third major potential source of carcinogenic BaP is the production and combustion of synthetic fuels or "synfuels" (*5*). Synfuels include fuels derived from the liquifaction or gasification of coal, oil shale, and tar sands. According to EEA (*30*), synfuels are potentially large sources of polycyclic organic compounds (such as BaP) because the desired gaseous or liquid product is one which contains a large proportion of combustible organic matter.

Based on limited data available, Guerin (*5*) has estimated that an industry processing 10^6 tons of coal per day will produce approximately 100 metric tons (110 tons) of BaP each year. He states that coal- and shale-derived crude oils contain two to three times more BaP than petroleum crudes and characterizes synfuels as a "potentially massive" new source of environmental PAH's (*5*).

In June 1980, Congress enacted legislation to create a twenty billion dollar synthetic fuel program for the U.S. aimed at producing 2.0 million barrels per day by 1992. The "Synfuels" Bill provided that Congress can act on an additional 66 billion in 1986. Federal financing has been approved for three commercial scale projects.

Citing a lack of adequate understanding of both emissions and the effect of controls for synfuels, EPA and the Department of Energy hazard no estimation of future levels of BaP from synfuels combustion (*30, 37*). Nor are there more than rough

estimates of future BaP levels from increased coal burning or diesel fuel combustion because of the shortcomings of the data described earlier.

Concentrations in Air and Particle Size Distribution

Ambient Air Concentrations. Available data on ambient concentrations of BaP are also of limited value in estimating health hazards. These data are largely confined to several large-scale monitoring studies by Sawicki and co-workers in 1958 and 1959 and data collected by the National Air Surveillance System (NASN) between 1966 and 1972 (*17*). The NASN data consist of those from 250 stations from 1966 to 1970 and only 40 stations between 1970 to 1972 (*27*). Large areas of the United States have never been monitored for BaP (*30*).

Table 2 gives BaP values for U.S. communities and selected cities including those measured in highly polluted air, cigarette smoke,* soil, and water for comparison. Particularly striking is the wide range of concentrations among communities studied (0.05–75 ng/m^3 in 1958) which is masked by the annual average figure of 6 ng/m^3 for the same year. Data collected in 1959 by Sawicki (*39*) (Table 3) give a better idea of the great intercity differences in BaP that existed primarily due to heavy coal burning in cities like Montgomery, Alabama, and Altoona and Youngstown, Pennsylvania.

According to EPA, annual average BaP air concentrations were reduced significantly between 1966 and 1972—by 55% in coke oven cities and 77% in non-coke oven cities (*27*). Yet in 1975, EPA stated that annual average seasonal concentrations still ranged from less than 1 ng/m^3 in nonurban areas to 50 ng/m^3 in urban areas with short-term or local concentrations reaching as high as 100 ng/m^3 (*17*).

*One cigarette contains an estimated 10-50 nanograms (ng) of BaP so that cigarette smoking—even so-called "passive" smoking—is a concentrated source of the pollutant (*4*).

Table 2. Measured concentrations of benzo(a)pyrene.

	BP concentration	Year	Reference
Air (ng/m^3			
U.S.A. (100 large urban communities)	0.05–75	1958	(*7*)
U.S.A. (100 large urban communities)	6.6	1958–59	(*38*)
U.S.A. (33 large urban communities)	3.3	1966–67	(*38*)
U.S.A. (large cities):			
Winter	6.0–74.0	1967	(*38*)
Summer	0.3–6.0		
U.S.A. (121 urban NASN sites)	2.4	1968	(*27*)
	2.3	1969	(*27*)
	2.0	1970	(*27*)
U.S.A. (nonurban sites)	0.4	1959	(*39*)
U.S.A. (cities with coke ovens)	4.7	1966	(*27*)
	2	1972	(*27*)
U.S.A. (cities without coke ovens)	2.8	1966	(*27*)
	0.6	1972	(*27*)
U.S.A. (selected cities)			
New York City	4.1	1966 (ann. avg.)	(*17*)
" " "	3.6	1969 (ann. avg.)	(*17*)
" " "	3.0	1970 (ann. avg.)	(*17*)
" " "	0.1–3.5	1976 (2 wks.)	(*40*)
Buffalo	4.2	1969 (ann. avg.)	(*17*)
Pittsburgh (heavy coal use)	14; 6	1969; 1970 (ann. avg.)	(*17*)
Birmingham (heavy coal use)	18	1966 (ann. avg.)	(*17*)
Great Britain:			
London	≤ 54	1968	(*7*)
Liverpool and North Wales	7–77	1954–55	(*41*)
Belfast	18–37	1961–62	(*7*)
Japan: Osaka	26 (rural) – 79.0 (urban: extreme values)	1968	(*42*)
Air: Highly Polluted (ng/m^3)			
Urban traffic	2.5–6.5		(*38*)
Tunnel	690		(*38*)
Coal-fired power plant (workers' atmosphere)	~30–390		(*38*)
Coke oven	216,000		(*38*)
Battery	16,000		(*43*)
Topside	18,000		(*44*)
Side and bench	7,000		(*44*)

Table 2 cont.

	BP concentration	Year	Reference
Gas works			
retort houses	3,000		(*38*)
above retorts	220,000		(*38*)
Roof tarring	14,000		(*38*)
Cigarette smoke (μg/100 cigs.)	0.5; 1.0; 1.2; 2.0; 7.5–12.5		(*38*)
(ng/cig.)	10–50		(*4*)
(ng/20 cigs.)	400 (avg. for filtered and unfiltered)		(*44*)
	700 (unfiltered)		(*44*)
	600 (unfiltered)		(*8*)
Urine of smoker (ng/l.)	0.55		(*45*)
Water (μg/m^3)			
Drinking	0.1–23.4		(*6*)
Surface	0.6–114		(*6*)
Soil (μg/kg)			
Nonindustrial	0–127		(*6*)
Towns and vicinities	0–939		(*6*)
Polluted by coal-tar pitch	650,000		(*6*)
Food (μg/kg)			
Meat			
Barbecued	2.6–11.2		(*6*)
T-bone steak	50.4		(*6*)
Smoked meat	0.02–14.6		(*6*)
Meat; sausage (broiled)	0.17–0.63		(*6*)
Vegetable oils			
Crude	0.9–15		(*6*)
Refined	0.4–36		(*6*)
Margarine	0.2–6.8		(*6*)
Vegetables			
Tomatoes	0.2		(*6*)
Salad	2.8–5.3		(*6*)
Spinach	7.4		(*6*)
Fruit			
Apples	0.1–0.5		(*6*)
Other	2–8		(*6*)
Cereals	0.2–4		(*6*)
Beverages			
Coffee	0.1–4.0		(*6*)
Tea	3.9–21.3		(*6*)

Table 3. BP concentrations in urban sampling sites for January through March 1959.[a]

High BP		Low BP	
Urban sampling site	BP, ng/m^3 air	Urban sampling site	BP, ng/m^3 air
Montgomery, Ala.	24	Little Rock, Ark.	1.5
Indianapolis, Ind.	26	Glendale, Calif.	0.8
Des Moines, Iowa	23	San Jose, Calif.	0.6
Portland, Maine	21	Miami, Fla.	1.9
St. Louis, Mo.	54	Shreveport, La.	0.7
Charlotte, N.C.	39	Jackson, Miss.	1.2
Cleveland, Ohio	24	Las Vegas, Nev.	1.4
Youngstown, Ohio	28	Bismarck, N. Dak.	0.4
Altoona, Pa.	61	Tulsa, Okla.	1.0
Columbia, S.C.	24	Dallas, Tex.	1.4
Chattanooga, Tenn.	31	Houston, Tex.	1.6
Knoxville, Tenn.	24	Salt Lake City, Utah	0.5
Richmond, Va.	45	Burlington, Vt.	1.0
Wheeling, W. Va.	21	Cheyenne, Wyo.	1.2

[a]Data of Savicki (*39*).

As with BaP emissions data, it is very important to recognize the inability of existing ambient monitoring data to reflect even substantial increases or decreases in concentrations of deeply respirable fine particulate BaP. This is because the BaP measured is that separated from total particulate material collected rather than that associated with fine particulates (*46*). The method of sampling involves extraction of solvent soluble organics from a portion of the high volume sampler filter on which are collected all particles from 0.002-500 μm in diameter. Therefore, preferential control of the numerically fewer large particles containing BaP could cause a decline in ambient BaP as currently measured without any real reduction in health hazard. Hence, one must view data on BaP trends with caution in assessing health risk.

On another level, the accuracy and precision of the analytical methods used to measure ambient BaP are such that levels reported in Tables 1 and 2 may be in error by at least an order of magnitude. Significant loss of BaP (as high as 15-40%) can occur by evaporation and photodegradation during collection, storage (for purpose of pooling samples), and analysis (*47*). Estimates of the accuracy of ambient analytical methods range from ± 25% (*9*) to ± 200-400% (*15*). The need to improve BaP monitoring and analytical methods to give accurate particle size-related BaP concentrations is especially urgent in light of anticipated increases in emissions (*5, 21*).

Particle Size Distributions. Investigations of the size distribution of BaP-containing particles consistently show that the great majority of BaP is associated with particles smaller than 1-2 micrometers in aerodynamic diameter and is therefore capable of penetrating into the alveoli. [For purposes of classification, particles are assigned a functional (aerodynamic) diameter equivalent to that of a spherical particle that settles at the same rate as the particle considered.] In the Pittsburgh area, more than 75% of the mass of PAH is in the form of particles less than 2.5 μm (*48*), while in Budapest, as in Canadian cities studied, the majority of PAH was associated with fine particles (*49-51*).

Nevertheless, certain sources can emit substantial amounts of BaP in association with larger nonrespirable size particles. In fact, according to Sawicki (*38*) Masek has reported that non-respirable dust fractions monitored at several coking plants contained more BaP than the respirable fractions (*52*). According to Natusch and Tomkins, however, in emissions from coal-fired power plants, BaP is preferentially adsorbed onto the surface of fine fly ash particles in the stack along with various toxic and carcinogenic trace elements (*18, 53*).

As illustrated in Figure 1, the size distribution of BaP is especially relevant to assessment of health hazard in that most of the substance is found in the particulate most likely to be deposited in the bronchioles and alveoli of the lung (*28*). Clearance of particulate from this compartment of the lung (mainly by macrophages) is relatively inefficient—ranging in time from days to years (*56*). Clearance is measurably impaired by cigarette smoking. For example, smokers who inhaled particles with a mass median aerodynamic diameter of 2.8 μm retained about five times more dust than nonsmokers a year after inhalation (*57*).

Other Physical and Chemical Properties Relevant to Biological Effects

Stability in the Atmosphere and Long-Range Transport. BaP is removed from the atmosphere by reactions with atmospheric oxidants, sulfur oxides and oxygen (*4, 9*). According to Kotin and Falk (*28*), however, BaP is relatively stable in air: even in a strong oxidizing atmosphere its rate of disappearance is lower than that of many other hydrocarbons. Depending on the presence of sunlight and the nature of the carrier particle, the half-life of BaP may range from less than a day to several days (*4*).

Particles of 0.1–1 μm size may have mean atmospheric residence times of one week to several months (*58, 59*). Evidence of the long atmospheric residence time of fine particulates is the observation of polycyclic organic matter derived from human activity as far as 2500 km from its source (*60*). The potential hazard from long-range transport of BaP and other organics has received far less attention than that of acid sulfate and nitrate fine particles also arising from the combustion of fossil fuels. Long range transport means that BaP is a more widespread pollutant than previously thought whose levels will increase alongside those of SO_2 and NO_2.

Elution of Benzo(a)pyrene. Another important property of BaP is that the substance is both readily adsorbed on the surface of soot and flyash and efficiently eluted upon deposition in the lung (*4*). Animal studies have demonstrated that BaP dissolves out of the carrier particulate into the macrophages and surrounding tissue (*61*). Elution is rapid and extensive for particles larger than 0.04-0.1 μm, increasing with particle size (*4, 28*). According to Coffin, the slower rate of BaP elution from the very small particles allows a slow, steady release of BaP to the target tissues which may increase the carcinogenic effect (*62*).

Elution may take place after transport to other sites of the lung. Saffiotti and colleagues (*63*) have

demonstrated in experimental animals that the macrophages carry BaP-containing particles from the peripheral lung, where they are deposited, to the upper segments of the respiratory tract. BaP is then eluted from the macrophages with resultant tumors of the upper respiratory tract. Thus in attempting to clear BaP from the lung, the macrophages serve to concentrate the carcinogen in one area of the lung.

Toxic Effects: Carcinogenicity

Introduction

The primary route of general human exposure to BaP is inhalation, although in occupational situations (e.g., coal tar plants, roofing, and roadbuilding operations) skin contact with BaP and related pollutants is important and has resulted in skin cancers, dermatitis, and photoallergy (*4*). BaP causes chronic effects in the lung, of which the most significant is lung cancer. There is, however, evidence that POM including BaP—in combination with other pollutants—may cause chronic bronchitis and emphysema. This evidence comes mainly from epidemiological studies of gas and coke oven workers (*15*) as well as from investigations of the general population showing increased nonneoplastic chronic respiratory disease in polluted urban areas (*64*, *65*). Because lung cancer is the toxicological effect of greatest concern (*6*), this section will focus on animal and human data most relevant to that effect. In order to better understand the significance of various studies discussed, it is useful to devote some attention first to the basic mechanisms by which BaP is now understood to act.

Metabolism of BaP

A large and coherent body of information on the metabolism of BaP has been developed since the 1930's. This work has been carried out largely in the rodent and in the human—in the whole animals, cells and organs in culture, and various tissue preparations. According to Sims and others, the overall pattern of metabolism in species and

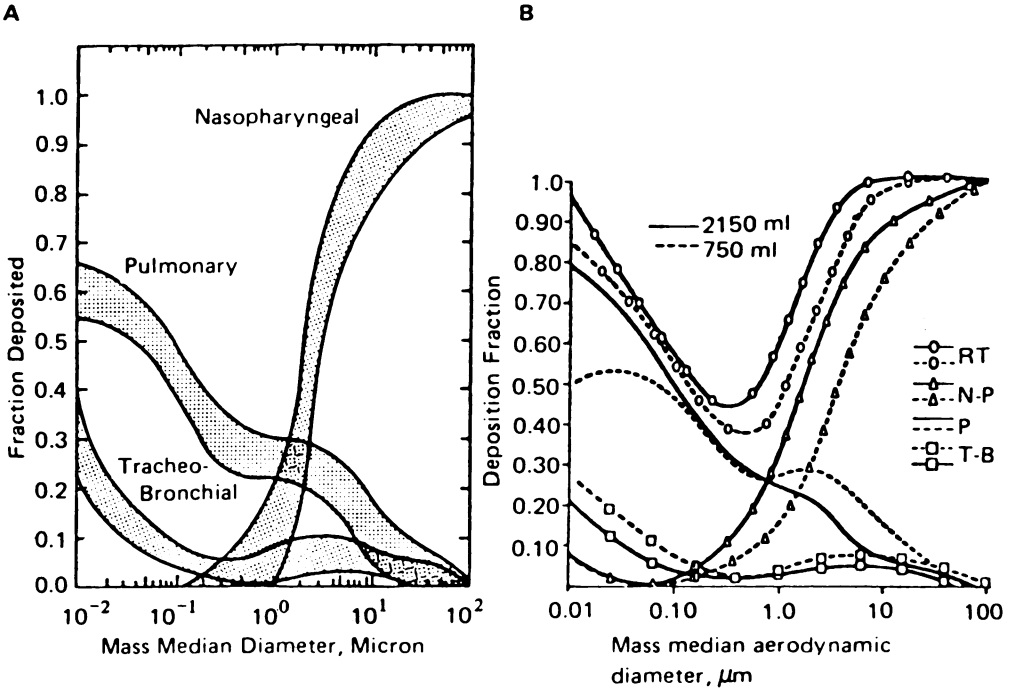


FIGURE 1. Predictions of deposition of particles in the lung. Regional deposition predictions based on the widely used model proposed by the International Commission on Radiological Protection Committee II Task Group on Lung dynamics indicating effect of variations in o_g and flow rate. (*A*) Each of the shaded areas indicates the variable deposition for a given mass median (aerodynamic) diameter in each compartment when the distribution parameter o_g varies from 1.2 to 4.5 and the tidal volume is 1450 ml. (*B*) Two ventilatory states, 750 and 2150 ml tidal volumes, (ca. 11 and 32 l./min volumes, respectively) are used to indicate the order and direction of change in compartmental deposition that are indicated by such factors. The tidal volume (the volume of air that is inspired and expired) is an important respiratory parameter. The deeper inhaled air goes and the longer it stays, the greater the deposition of particles (*54*, *55*).

systems tested is the same (*66*, *67*).

As early as the 1950's, animal studies showed that BaP is covalently bound to DNA, RNA, and proteins of the cells in target tissues (*68*). In 1964, Brookes and Lawley demonstrated that the extent of covalent binding of polycyclic aromatic hydrocarbons to DNA in mouse skin was correlated with carcinogenic potency (*69*).

In 1966, the Millers from the University of Wisconsin Medical Center discovered that a number of chemical carcinogens exert an effect only after metabolic activation *in vivo* to an electrophilic form capable of reacting with nucleophilic residues in protein and nucleic acids to form covalent adducts (*70*, *71*). The overall metabolism is summarized in Figure 2. Their work and that of other researchers has brought wide acceptance of the general concept that most chemical carcinogens act through strong electrophilic metabolites able to bind covalently to cellular macromolecules, the most probable target being DNA (*68*, *72*). Considerable evidence suggests that covalent adduct formation represents both the initial and critical step in chemical carcinogenesis (*72-74*).

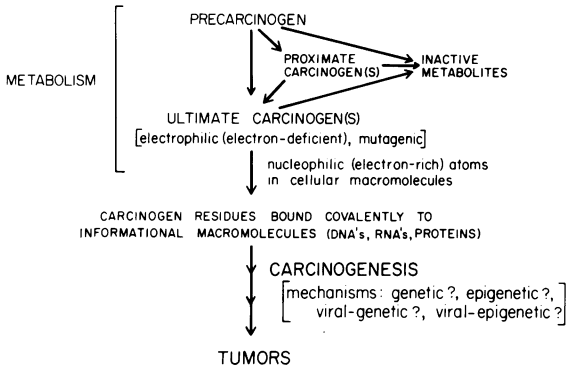


FIGURE 2. Overall metabolism of the majority of chemical carcinogens (*75*).

The requirement for metabolic activation was directly illustrated for BaP by two independent researchers who found that when BaP is incubated in a test tube with DNA, binding does not occur until addition of the microsomal mixed function oxidase system (MFO) (*68*, *76*, *77*). More recently, negative results for BaP using several *in vitro* test systems for mutagenicity in the absence of microsomal preparation have illustrated the importance of metabolism by the MFO (*78*, *79*).

In 1957, Conney and colleagues described the oxidative metabolism of PAH by enzymes located in the endoplasmic reticulum (*80*). Since then, this enzyme system has been shown to consist of sev-

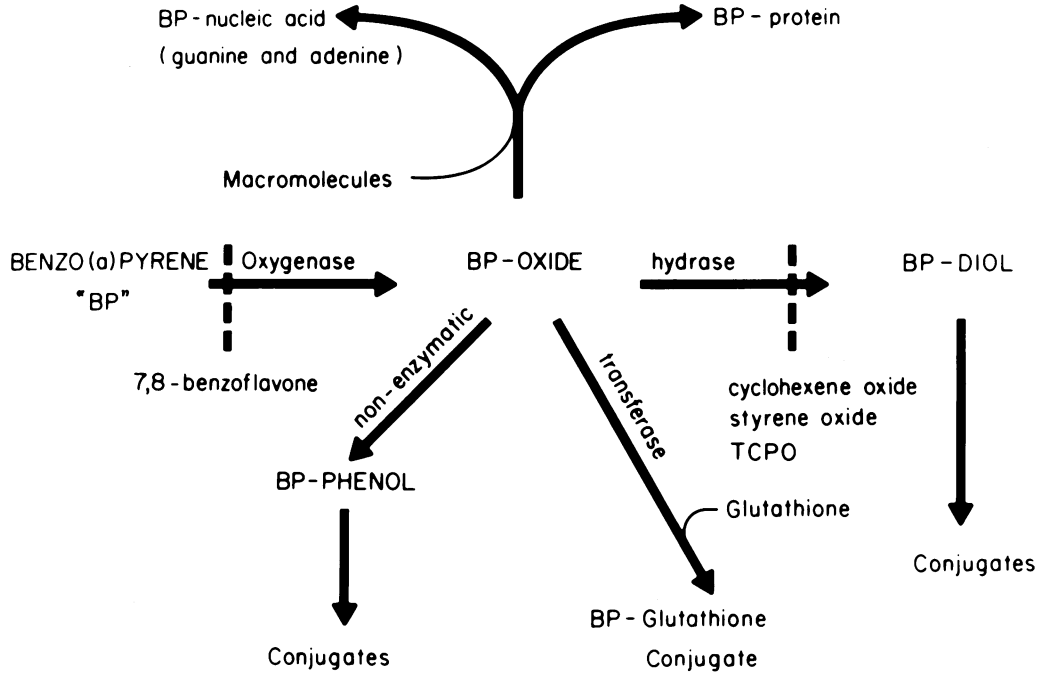


FIGURE 3. Microsomal metabolism of BP, leading to detoxification products and to nucleic acid binding. BP-protein and BP-nucleic acid designate the reaction products of BP with protein and nucleic acid respectively; TCPO = trichloropropylene oxide. Current evidence indicates that BP = 7,8-diol can recycle through the oxygenase system to form the oxide BPDE. BPDE is the major BP metabolite involved in nucleic acid binding (*73*).

eral forms of cytochrome (P-450) and an electron transport chain. The function of the P-450 or aryl hydrocarbon hydroxylase (AHH) is to catalyze the oxidative metabolism of BaP (as well as other xenobiotic and even some endogenous compounds) in order to eliminate these substances (*81*). This is accomplished through conversion of the initial lipid soluble substance to a more water soluble form that can be excreted or conjugated with more polar groups and then excreted (*73, 82*) (Figure 3).

As shown schematically in Figure 3, the initial intermediates in this oxidative process are epoxides which alternatively hydrate by an enzyme-epoxide hydrase (EH) to dihydrodiols, rearrange to phenols, or react with glutathione. Once dihydrodiols are formed, they are either further oxygenated to diol epoxides, or are conjugated with water soluble entities and removed (*73, 79, 83, 84*).

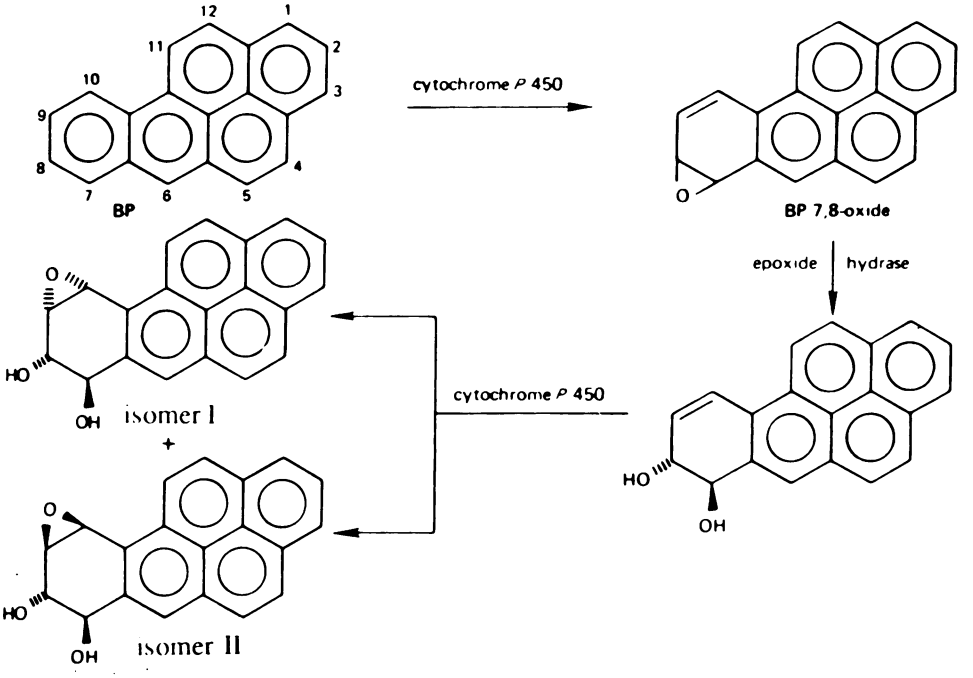
The diol epoxide intermediates are capable of reacting with cellular nucleic acids and proteins to form covalent adducts. Thus, ironically, in carrying out the basic function of detoxifying BaP, the MFO causes a fraction of them to become active carcinogens.

The MFO level and activity are altered by a variety of drugs, pesticides, food additives, steroids and even by exposure to particles and cigarette smoke (*85, 87*). Enzyme activity is also affected by age, sex, hormonal balance, nutritional status, and genetic factors (*88*).

The MFO's are present in most mammalian tissues and have been identified in the liver, placenta, lymphocytes, monocytes, and lung macrophages in humans (*79*). Of possible significance is the recent finding that the cytochrome P-450 system is localized in the nonciliated bronchiolar epithelial cells of the small airways of the rabbit lung at much higher concentrations than in other organs or cell types studied. According to the authors, this might be an important determinant in the susceptibility of the lung to a number of toxic chemicals that require metabolic activation (*89*).

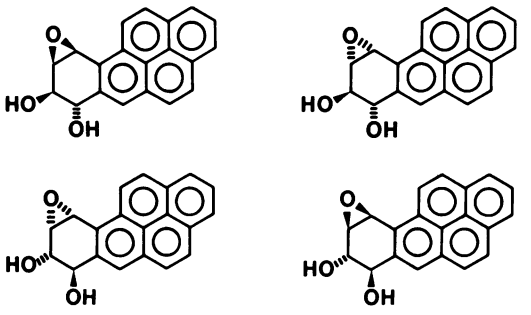
As early as 1950, Boyland proposed an epoxide intermediate for carcinogenic PAH (*90*). Over the past seven years, studies in Great Britain and the U.S. have indicated that the critical metabolite of BaP is not a simple oxide but a dihydrodiol epoxide capable of interacting with tissue constituents —not at the K-region as initially thought —but at the oxygen situated in the bay region (*91*) [Eq. (2)].

According to Miller (1978), elegant studies from the laboratories of Brookes, Conney, Gelboin, Harvey, Jerina, Sims and Grover, and Weinstein now implicate diol epoxide I [7,8-dihydroxy-9,10-epoxy-7,8,9,10-tetrahydrobenzo(a)pyrene, also known as diol epoxide 2, BPDE I, BPDE 2, and "anti-isomer" due to inconsistencies in terminology among different laboratories] as a major ultimate electrophilic, mutagenic and carcinogenic metabolite of BaP whose major reaction products involve the 2-amino group of guanine residues and C-10 of the



(2)

epoxide and to a lesser extent, adenine and cytosine residues (*72*).



r-7,*t*-8-dihydroxy-*t*-9,10-oxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene diol-epoxide I *anti* isomer

r-7,*t*-8-dihydroxy-*c*-9,10-oxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene diol-epoxide II *syn* isomer

(±)7α,8β-dihydroxy-9β,10β-epoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene

(±)7β,8α-dihydroxy-9α,10α-epoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene diol-epoxide 2

(±)7α,8β-dihydroxy-9α,10α-epoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene

(±)7β,8α-dihydroxy-9β,10β-epoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene diol-epoxide 1 (3)

Recently, the complete chemical structure of the major adduct formed between benzo(a)pyrene diol epoxide (BPDE) and cellular nucleic acids has been shown to be that in Figure 4 (*92*, *93*). The adduct pictured results from the binding of the antiisomer or diol epoxide I. It is the predominant adduct consistently found in mammalian and human cells exposed to BaP *in vitro* (*94*).

Unlike acetylaminofluorine, which causes significant distortion in the DNA helix following displacement of a base in the DNA, BaP bound to guanine appears to be accomodated outside the DNA helix—probably in the minor groove as in Figure 5B (*95*). This accomodation may explain the relative persistence of the adduct in that the cell does not single out minor distortions for repair.

It is not known whether the consequence of BaP-DNA binding is a genetic, epigenetic, or yet another change that results in carcinogenesis (*96*). The possible outcomes are the following: (1) DNA repair mechanisms are triggered: if prompt and error-free, no effect results from binding. (2) DNA repair mechanisms are triggered: if error-prone or delayed repair occurs, impairment in DNA template activity results in mutations in the daughter cell (*97*, *98*) or impairment in template activity results in interference with RNA transcription. This causes distortion in gene transcription and the pattern of gene expression (*73*).

The limited available information on the rate of repair of DNA following BaP binding indicates that efficiency of excision is poor: in one study using cultured human lung cells, 55% of the BPDE-I adduct remained 72 hr after exposure (*99*), while in two other investigations, 80% of BPDE-I-dG adduct was present in human lung cell cultures after 30 hr (*100*), and 35% remained in human bronchus cells after 10 days (*87*). In mouse skin cultures, little if any loss of BP-DNA adduct was

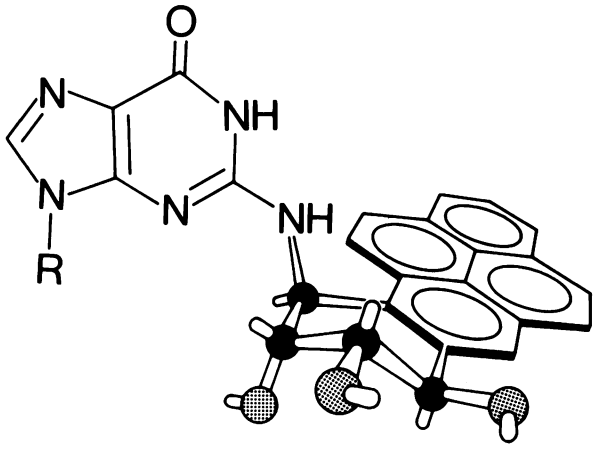


FIGURE 4. Schematic representation of the guanosine-BP adduct formed from the reaction of BP-diol epoxide I with polyG (*92*).

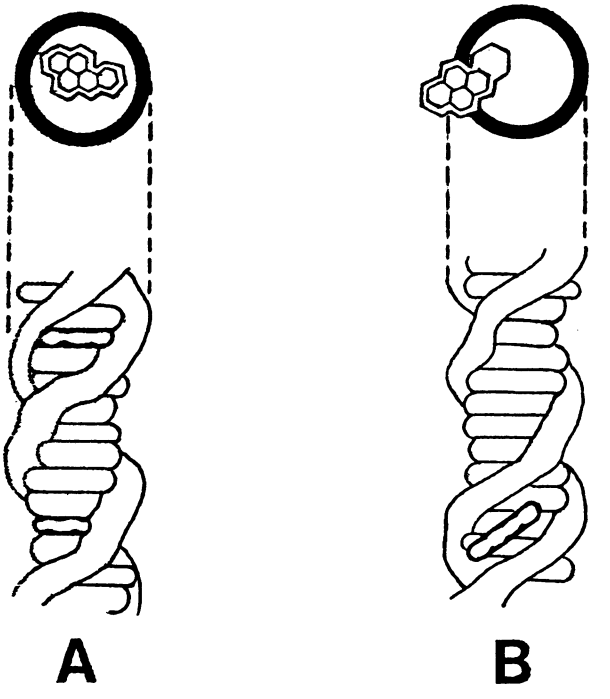


FIGURE 5. Schematic representations of a DNA double helix containing (*A*) benzo(a)pyrene physically bound by intercalation and (*B*) covalently bound benzo(a)pyrene diol epoxide residue lying in the minor groove of the helix (*95*).

observed for 49 hr (*101*). Similarly, Poirier et al. (*102*) observed approximately 40% removal of BPDE-I adduct after 23 hr in mouse epithelial cells in culture. Strauss and co-workers (*103*) estimated that about 0.5% of lesions are removed per hour, probably via the nucleotide excision pathway.

Studies of human cells in culture have demonstrated that covalent binding occurs in many types of cells: in lung cells (*104*), in pulmonary alveolar macrophages (*87*), in skin cells (*105*), in peripheral monocytes (*106*), and in pancreatic cells (*107*).

Second, the amount of adducts formed in human cells in culture is dependent on dose of BaP, and length of exposure, as well as the presence of certain binding inhibitors (benzoflavone and antioxidants such as vitamin E) as well as inducers (e.g., cigarette smoke, and benzo(a)anthracene) (*87*, *104*).

Third, human cell studies show broad interindividual variation in the amount of binding: 75-fold in cultured bronchial cells (*87*, *104*), and 44-fold in peripheral lung cells from lung cancer patients (*108*).

It has been suggested that genetic variations in the activity of AHH can be correlated with risk of lung cancer. Kellerman et al. have reported a trimodal distribution of AHH inducibility in cultured human lymphocytes of healthy individuals and lung cancer patients, with 96% of lung cancer patients having intermediate or high AHH activity as compared with 55% of healthy individuals (*109*). The authors suggested that people with high AHH activity are at greater risk of lung cancer because they produce more carcinogenic epoxides than the low AHH group (*110*). Work by Trell et al. with laryngeal cancer patients would seem to confirm this finding (*111*).

However, much subsequent research has not supported this theory. Paigen et al. (*112*, *113*) have carried out a series of studies of the role of AHH in relation to cancer risk and failed to find a genetic tendency to high AHH inducibility (that could be passed on to their children) in patients with lung or laryngeal cancer. According to Gurtoo et al. (*114*) the AHH assay predominantly measures phenols rather than the carcinogenic metabolites. Induction of the proximate carcinogen also does not parallel that of phenols. Therefore, citing Miller (1978), they conclude (*114*): "A more direct measure of BP activation to carcinogenic metabolites could be a DNA-binding assay, since DNA binding may be a critical step in tumor initiation by chemical carcinogens." This is an echo of an earlier complaint about uncertainties in estimating the effect of BaP in air pollution. A task group convened to assess the relationship between lung cancer and air pollution stated (*10*): "This estimation process could be substantially improved if measurements could be made of levels of ultimate carcinogen at the point of activity (perhaps the nucleus of target cell) both experimentally, and in man . . ."

Recently, Poirier et al. (*102*) have developed an assay which can estimate the amount of BP-DNA adduct in tissue using a competitive radioimmunoassay technique. According to the authors (*102*), this method may provide a tool for use in epidemiological studies investigating the "biological consequence of human exposure to specific chemical carcinogens through assay of DNA from cells and from tissues of exposed individuals."

Experimental Evidence of Carcinogenicity of BaP

Animal Studies. Animal data show BaP to produce tumors in all nine species for which data is reported and by all routes of administration. Work with experimental animals has elucidated the metabolism and the dose-response relationship of BaP and has allowed a partial understanding of the mechanisms involved in carcinogenesis. The vast literature has been well reviewed by the NAS (*4*) and the IARC (*6*).

Investigations using experimental animals have demonstrated several principles relevant to the role of ambient BaP in lung cancer.

(1) BaP is an initiating carcinogen whose effect is enhanced or promoted by various other chemical substances. BaP has been shown to be a potent carcinogen effective in a single dose and, when administered transplacentally, able to cause cancer in the offspring after birth (*6*). Skin painting studies have demonstrated that induction of cancer by low doses of BaP is a multistep process: in one experiment, a single low dose of BaP to mouse skin produced no tumors, while subsequent treatment with a promotor (phorbol ester) produced carcinoma (*115*).

In the environmental situation, BaP is found in conjunction with SO_2 and other irritant gases and particles capable of enhancing its effect. Laskin et al. (*116*) have produced excess squamous cell carcinomas in rats exposed by inhalation to 10 mg/m^3 of BaP plus 3.5 ppm SO_2 by further increasing the exposure to SO_2. The authors believe that these findings are significant since both materials are found in community air, and exposure of animals resulted in the type of carcinoma predominantly found in man. This study suggests that SO_2 acts synergistically with BaP by slowing ciliary action

and increasing BaP retention and/or by causing chronic injury to the cell so that regenerating cells are more susceptible to the carcinogen (*15, 117*). According to Hoffmann and Wynder, in addition to SO_2, 18 substances identified in urban air are toxic to the lung's mucociliary clearance system; these include formaldehyde, acrolein, and phenols (*7*). Nitrogen oxides (*118*) as well as certain acid sulfates and nitrates are strong irritants (*119, 120*) and could also act to enhance the carcinogenic action of BaP.

(2) The carcinogenic effect of BaP is related to dose; no study has demonstrated a threshold dose for BaP; and the effect of low, divided doses may be greater than that for a single high dose. Montesano et al. (*121*) and Feron et al. (*122*) have observed a dose-response in hamsters given increasing levels of BaP and ferric oxide. In the latter study, a clear dose-response relationship emerged with the lowest dose of 3.25 mg total per lifetime, eliciting a 10% response in the exposed animals compared with 0% incidence in controls. Yanysheva and Antomonov (*123*) reported excess tumors in rats exposed to a total dose of 0.5 mg. In an earlier dose-response study with BaP and hematite, Saffiotti and co-workers (*124, 125*) observed excess tumors at the lowest dose of 0.25 mg BaP per week with 11% of the animals affected. This investigation failed to demonstrate a no-effect level (*6*).

Analysis of BaP retention rates in hamsters show that the carcinogen is eluted more rapidly from the carrier particulate when given in small doses (*126*). This may explain why low doses of BaP have been more effective per unit dose in several studies. Studies by Saffiotti et al. (*124-126*) indicated that a given total amount of BaP combined with iron oxide produced tumors earlier when given in small divided doses by frequent instillations than when given in a single administration. For example, when Saffiotti, Montesano, and colleagues administered a single dose of 5 mg BaP with ferric oxide intratracheally, they found a 4% incidence of respiratory tumors with the first tumor appearing at 52 weeks (*124, 125*). By contrast, when they fractionated a total dose of 5 mg BaP into 20 administrations, an 11% incidence resulted; the first tumor was found at only 22 weeks. Similarly, a total benzpyrene dose of 0.1 mg administered to rats once and in five fractions did not produce tumors, but a tumorigenic effect was seen when 0.1 mg was administered in ten fractions (*123*). The Task Group (*10*) cites further evidence of this effect in the work of Bryan and Shimkin (*127*), Yanysheva (*128*), and Payne and Heuper (*129*). The group considered these experiments showing enhanced effect of repeated, low doses of BaP to be relevant to their assessment of risk to humans from constant exposure to low levels of BaP in the atmosphere.

(3) Interaction between BaP and fine particulate particles results in an increased carcinogenic effect. Synergism has been demonstrated in animal studies in which BaP carried by particulates (such as carbon or iron oxide particles) produces a more pronounced carcinogenic effect than BaP alone (*4, 63, 121*). In studies with hamsters, Saffiotti and co-workers (*63*) observed bronchogenic carcinoma in all hamsters (surviving after 16 weeks) exposed to an equal mixture of BaP and ferric oxide particles, whereas ferric oxide particles alone did not produce any tumors.

Polluted air contains BaP and large quantities of fine particulates including carbon, hematite, and trace metals, all in the presence of irritant sulfur and nitrogen oxides, phenols, etc. (*130*). Coffin (*62*) has observed that the ingredients necessary for lung cancer in animals are present in urban air.

In Vitro Studies. Since the early 1970's, BaP has tested positive in over twenty *in vitro* short-term test systems considered to be predictive of potential human carcinogenicity (*133*).† These include assays for mutagenicity in bacterial and mammalian cell systems; tests for DNA damage; and assays for cell transformation. In all of these systems, metabolic activation using enzymes or cocultivation was necessary. Extracts of airborne particulate—of which BaP is a component—have also given positive results in *in vitro* tests for mutagenicity/carcinogenicity (*134*). Recently, Tokiwa et al. (*135*) studied the mutagenicity of various size fractions of airborne particulate collected at an industrial site; they found that the size range 0.1-0.3 μm in diameter contained the highest concentration of BaP and was of maximal mutagenic activity in the Ames assay.

Extracts of diesel particulate, which contain significant amounts of BaP, have given positive results in an array of short-term *in vitro* tests (*136, 137*). Most studies have been made of diesel particulate extract rather than diesel particulates themselves. However, McCormick (*138*) has reported that diesel particulates incubated with normal human cells and with DNA-repair deficient (XP) human cells, respectively, caused differential toxicities. These results indicated that substances capable of

†For example, mutagenicity in the Ames *Salmonella typhimurium* bacterial assay is widely considered to be an indicator of carcinogenicity because of the high correlation (around 90%) between the two effects (*131*). Purchase et al. (*132*) found a similar correlation between transformation of cells in culture and carcinogenicity.

damaging human DNA were eluted off the particle within the cell.

Mutagenicity/carcinogenicity of various BaP metabolites has been demonstrated in numerous *in vitro* assays from the early 1970's on, allowing comparisons of potency. For example, Jerina and colleagues (*139*) have reported higher mutagenicity in 7,8-diol-9,10-epoxides of BaP and 7,8-dihydrodiol compared to other derivatives of BaP tested *in vitro*. Other short-term assays for mutagenicity have been positive for BaP. For example, Rudiger et al. (*105*) reported that BaP induces sister chromatid exchange in cultured human lymphocytes.

In 1965, Berwald and Sachs reported that cells transformed by PAH produced tumors when injected into the whole animal (*140*). Investigators have subsequently shown a direct relationship between the extent of transformation in cultured cell colonies and carcinogenic potency (*4*). Extracts from both urban and workplace air and BaP itself have also transformed cells *in vitro* (*4*, *15*). A recent study reported that cigarette smoke extracts enhanced transformation of cultured cells exposed to benzo(a)pyrene (*141*).

Human Evidence of the Carcinogenicity of BaP

Concerning epidemiological evidence on the carcinogenicity of BaP, there are numerous epidemiological studies of workers exposed to mixtures of BaP and other pollutants; a body of data relating to the effects of general air pollution; and, of course, the vast literature on smoking. All are relevant to the inhalation toxicology of BaP since all three situations involve exposure to BaP as a potent initiating carcinogen in combination with irritant, ciliatoxic, and carcinogenic ingredients (*7*, *15*, *142*).

The results of studies of workers exposed to BaP in a mixture of pollutants released during coal gasification, coke oven and roofing operations show a dose response with relative risks of 33-fold in Japanese gas workers (*143*) and 16-fold in coke oven workers with the highest cumulative exposure, compared to unexposed controls (*15*, *144*, *145*). Epidemiological investigations of workers exposed to diesel emissions are inconclusive to date because of methodological problems including failure to allow for the latency period of lung cancer (*146*) (Table 4).

There have been no detailed epidemiological studies of community exposure to industrial sources of BaP. Suta (*150*) has estimated, however, that the 17 million people living near coke ovens in the U.S. inhale from 3-1,500 ng BaP annually and about half inhale greater than 100 ng BaP daily.

A number of epidemiological studies have compared the lung cancer experience of people living in areas with differing levels of BaP and related pollutants (*42*, *151-155*). All but Higgins (*154*)

Table 4. Summary of epidemiological studies of workers exposed to diesel emissions.

Effect and population studied	Exposure classification	Results	Caveats	Reference
Mortality and morbidity in London Transport staff exposed to diesel; men aged 45–64 were studied from 1950–54	Men were grouped in order of estimated exposure to exhaust fumes based on general observation and not chemical estimation	A total of 96 deaths were from lung cancer, ill-health retirements, and transfers due to lung cancer; highest rate was in 2nd least exposed group (trolleybus engineering staff); no excess was found in highly exposed group; association was found with place of residence	The number of cases was very small; the study did not take into account the long latency period of lung cancer; smoking histories were not taken	(*147*)
Mortality in U.S. railway workers; 154 deaths between 1953–58 due to cancer of lung and/or bronchus were studied	Workers were divided into 3 groups based on estimated exposure	The least exposed group had the highest lung cancer mortality; an association was found with residence in urban areas	Selection in retiring ill employees was not evaluated; smoking was not considered; other causes of death which compete with lung cancer were not evaluated; small number of deaths	(*148*)
Mortality in potash workers from 8 mines—2 dieselized—was studied for the period 1940–1967	Workers in dieselized mine were compared with non-dieselized	No excess mortality from lung cancer was found in exposed workers	Mines dieselized only since 1949 and 1957 (insufficient time for induction?); small number of deaths (31) may preclude significant results	(*149*)

found a significant correlation between lung cancer mortality and BaP and/or related pollutants.

Stocks (*151*) compared lung cancer death rates in Liverpool and rural North Wales. BaP levels were 77 ng/m^3 and 7 ng/m^3 in the respective areas. Compared with their counterparts in North Wales, nonsmokers in Liverpool had a 127% excess in lung cancer mortality or 28 extra deaths per 100,000 population. For smokers of one-half a pack daily, the increase in the urban residents was even greater: 143% or 100 additional deaths per 100,000. These data suggest that the effect of air pollution and cigarette smoking is synergistic rather than additive (*8*).

Another investigation by Hitosugi concluded that there was an 80% increase in lung cancer death rates in the residents of the area with high BaP pollution when age and smoking were taken into account (*42*). No differences were seen in rates for non-smokers (possibly because of the small numbers of deaths in this category), but smokers in the high BaP area experienced 80-120% higher death rates compared to those in the less polluted area.

These figures must be regarded as estimates only because of the many potential confounding variables and the inadequacies in monitoring data. For reasons mentioned earlier, there may be significant errors in the air concentration levels on which the studies are based. According to the OTA, if the errors in air monitoring are random, they could result in a significant understatement of the effect on health (*21*).

A dose response has been clearly demonstrated for cigarette smoking and lung cancer (*156*, *157*). Based upon results of epidemiological studies, Wynder and Stellman (*158*) estimate the relative risk of lung cancer to be as great as 18 for nonfilter smokers of 1-10 cigarettes daily compared with nonsmokers.

Pike et al. (*8*) compare the amount of BaP a nonsmoker in 1959 would have inhaled daily from the ambient air of St. Louis, Missouri (810 ng), Montgomery, Alabama (360 ng) and Dallas, Texas (21 ng) with the amount of BaP inhaled by a smoker of one pack of nonfiltered cigarettes daily (600 ng). They conclude that "If a nonsmoker in Montgomery breathed the air as if he were smoking, then in terms of BaP taken in, it would be roughly equivalent to a smoker of one-half a pack daily in Dallas." Following this logic, and applying the relative risk derived by Wynder and Stellman (*158*) above, we could estimate that the risk of lung cancer for an individual non-smoker in Montgomery in 1959 was at least 18 times that of a non-smoker in Dallas. Of course, such a calculation assumes that BaP is a reliable and comparable index of carcinogenicity of both mixtures—cigarette smoke and air pollution.

Because the assumptions involved in such an extrapolation are so large, several investigators have turned to occupational and general population epidemiology in an attempt to develop estimates of the risk of BaP at levels encountered in ambient air (*8*, *152*). Using data from Stocks (*151*), Pike et al. have derived a dose response function for ambient BaP, i.e., that each increment of 1 ng/m^3 BaP causes 0.4/100,000 and 1.4/100,000 extra lung cancer deaths per year in nonsmokers and in smokers, respectively (*8*). The figure of 0.4/100,000 was consistent with Pike's calculations based on studies of British gasworkers carried out by Doll and co-workers (*159*). However, as can be seen from Tables 5 and 6 these exercises also entail large assumptions as well as uncertainties in the data and cannot, therefore, be accepted as anything more than range-finding.

Although these epidemiological studies do not provide the basis for quantitative risk estimates, they are consistent with two important findings of studies in experimental animals. First, the greater relative risk of lung cancer experienced by coke oven workers as compared with British gasworkers —16-fold versus twofold—may be a reflection of concurrent exposure to high levels of SO_2 in coke oven plants. By contrast, SO_2 was not far from the "normal" urban range in the gasworks.[15] This observation can be related to experimental findings of synergistic interaction between BaP and SO_2 in the production of tumors by Laskin et al. (*116*).

Second, as mentioned above, data of Stocks, Hitosugi and others point to a synergistic relationship between BaP and cigarette smoking (*8*, *160*). Further evidence is provided by a retrospective (case-control) study of lung cancer deaths in Japan that concluded that smokers in polluted areas had a 6-fold risk of lung cancer compared with nonsmokers; if atmospheric contamination was added to cigarette smoking, the risk of lung cancer increased to about tenfold. In the absence of smoking, the relative risk of lung cancer for those living in the high pollution area was only 2.5 (*161*).

Difficulties in Quantitative Assessment of Risks of BaP

Although EPA's proposed cancer policy for carcinogens in the air incorporates quantitative risk assessment as the basis for regulatory decision-making (*162*), the Clean Air Act Amendments of 1977 do not require such assessment before EPA can take action to regulate a hazardous or carcino-

Table 5. BP dose-response estimates derived from general air pollution epidemiology.

Estimate	Assumptions or comment	Reference
Increases in lung cancer death rate in smokers per BaP "unit" range from 10% (light), 5.5% (moderate), 1.1% (heavy) to 13% (nonsmokers). For moderate smokers a "unit" BaP was associated with an excess $104/10^5$ lung cancer deaths.	A unit BP is defined here as 7.0 ng/m^3 BP; therefore an excess 14.5 deaths/100,000 would be associated with 1 ng/m^3 BP. Average increase per ng/m^3 BP in smokers is 5.5%.	(*4*, *152*)
An estimated $1.4/10^5$–$0.4/10^5$ extra deaths are attributable to 1 ng/m^3 BP in smokers and nonsmokers, respectively.	Results for nonsmokers are remarkably consistent with those derived from British gas workers data; differences in duration of exposure might explain 3–4 times higher results obtained here for smokers in general population compared with smokers among gas workers.	(*8*)
A 4% increase in the lung cancer death rate in smokers is associated with 1 ng/m^3 BP.	Hitosugi recorded an average 60% increase in lung cancer mortality for smokers (120% for light smokers) in areas of high BP; the difference in annual average BP levels in high vs. low pollution areas was 16 ng/m^3 (estimated as 30% of yearly maximum). (For light smokers taken as a separate class, a 7.5% increase in lung cancer mortality was associated with a 1 ng/m^3 increase.)	(*4*, *152*)

Table 6. BP dose-response estimates derived from occupational epidemiology.

Estimate	Assumptions or comment	Reference
Extrapolation from observed excess $160/10^5$ lung cancer cases in British gas workers from exposure to the equivalent of 440 ng/m^3 BP in general air pollution gives an estimated $0.4/10^5$ extra lung cancer cases/yr per ng/m^3 BP in the general population.	Workers were exposed to 2000 ng/m^3 BP for about 22% of the year (assuming 40-hr. work week with 3 weeks annual leave); therefore exposure was 2000 × 0.22 or 440 ng/m^3 BP. Pike did not correct for the fact that gas workers were not exposed all their lives.	(*8*)
Based upon excess ($7118/10^5$) deaths by Lloyd among coke oven workers exposed to the general air pollution equivalent of 224 ng/m^3, a $24.7/10^5$ increase in deaths is associated with 1 ng/m^3 BP in the general population.	Author took 24% of minimum BP level measured on top of coke ovens; he assumed roughly the same relationship between worker and general population exposure as Pike (*8*).	(*155*)

genic air pollutant (*163*). Further, there are very real difficulties in performing quantitative risk assessment for BaP or any other airborne carcinogen using methods and data available at this time. For reasons already alluded to, the experimental and epidemiological data such as those described in the previous section allow the identification of BaP as an important atmospheric carcinogen but do not provide the basis for a reliable estimate of the magnitude of the risk because of the many sources of uncertainty and error in such an exercise.

Using Experimental Data. First, the reliability of extrapolation from data derived from animal studies to man is limited by the following uncertainties.

(1) Problems in Extrapolating from High Doses in Small Animals to Low Doses in Man. Mathematical models developed to extrapolate the results of high-dose, small-scale animal studies (necessary for practical reasons) to low-level exposure of the general public differ by a factor of 100,000 in projections of the dose that would cause one extra cancer in a million animals (*164*). According to Cornfeld (*165*), "no firm scientific basis now exists for choosing among them." Furthermore, despite the fact that the common assumption of a linear relationship between dose and response (*166*, *167*) is generally believed to be conservative, there is evidence that repeated lower doses of a carcinogen (and BaP specifically) are actually more effective than higher doses (*10*).

An additional problem is the need to "relate" doses in small animals to man. It is unclear whether this should be done on the basis of relative body weights, surface areas, lifespans, or some other method (*163*, *168*).

Inability to resolve such questions has led to the conclusion by the National Academy of Sciences (*169*) that the risk of consuming saccharin in one can of diet soda per day could lead to as few as 0.0007 cancers per year in 50 million people, or as many as 3,640. This is a range of error greater than a million-fold (*163*).

(2) Unknown Differences in Species Sensitivity and Possible Metabolic Differences among Species and Strains within Species.

Animal species can have marked differences in sensitivities to carcinogens—as great as two or more orders of magnitude. There is, in fact, evidence that man may be the most sensitive species to certain chemical carcinogens (*10*). Variation in sensitivity—combined with unpredictable differences in metabolic, pharmokinetic, and repair mechanisms between species—is a significant source of imprecision.

(3) Failure to Consider Interactions and Synergism between Environmental Agents. Whereas animal experiments are generally carried out with one test substance in a controlled environment, humans are exposed to a variety of interacting and synergistic agents. BaP is a prime example of an atmospheric carcinogen capable of interaction with other pollutants as well as factors such as smoking. The Council on Environmental Quality regards this factor to be a major obstacle to quantitative risk assessment (*170*).

(4) Failure to Consider Interindividual Variation in Sensitivity of Humans. There is no established method of measuring differences in human sensitivity to carcinogens; yet it is well known that humans are genetically heterogeneous and are therefore suspected to have a wide variation in response. By contrast, interindividual variation has been reduced or eliminated in most experimental lines by breeding in order to arrive at a genetically homogeneous test population. Therefore, the unknown but presumably broad range of human sensitivities is a source of uncertainty in extrapolating from animal data.

Using Human Data. Similarly, limitations of human epidemiological studies preclude reliance upon their findings for quantitative risk assessment. Undertaken as they are in a complex natural setting, epidemiological studies are hindered by a large number of variables that can obscure true relationships between a causal agent and disease (*171*, *172*). Further, because only limited study populations are generally available, it is difficult to detect modest increases in an effect such as lung cancer which may nonetheless be important in a large population (*173*). Even large-scale studies have limited ability to detect a real excess cancer rate of less than 50% (*174*).

Another frequent problem is the failure to consider the latency period of cancer (often on the order of decades) and concluding, wrongly, that no excess risk exists. Finally, in epidemiological studies involving environmental pollutants such as BaP, precise exposure or "dose" data are not available for the dual reason that monitoring data are inadequate and because duration of exposure is rarely known.

Based upon data from four epidemiological studies and three animal experiments, the CAG derived an estimate of 200 deaths per year nationwide attributable to POM (*175*). For all of the reasons just discussed, such a risk estimate must be viewed with caution.

The impossibility of quantifying the risk of BaP automatically precludes valid economic "cost benefit" analysis. Nor is balancing of costs and benefits required in regulating hazardous pollutants under Section 112 of the Clean Air Act. According to the OTA such an exercise would probably produce spurious results which would tend towards significant understatement of the benefits of regulating BaP because, whereas we know the economic costs of controls, we can not now know the environmental and health "costs" of foregoing controls (*21*).

Control of BaP

Inefficiency of Present Controls

Existing controls for stationary fossil fuel combustion sources are aimed at achieving weight-based emissions or ambient air quality standards for total suspended particulate matter and therefore tend to control coarse particles at the expense of the fine particulate component. For example, according to Kornreich, when high efficiency particulate controls are used together, 83% of the particles emitted are smaller than three micrometers in diameter (*176*). Pike et al. (*8*) have observed that "the bulk of BaP now in the air is associated with particles that do reach the lungs, but this was probably not true when large soot particles were still commonly present in the atmosphere." (p. 229).

Today 97% of power plants have cyclones, scrubbers, or electrostatic precipitators (ESP's), fabric filters, or a combination. Except for fabric filters, most applications of these technologies tend to be inefficient for very fine particles with which BaP is largely associated (*130*). Cyclones, for example fail to remove particles smaller than 10 μm; low energy scrubbers are inefficient collectors of fine particles (*30*) and electrostatic precipitators have a substantial drop in collection efficiency for particles below 0.5 μm (*177*). Furthermore, most BaP exists as vapor in the stack of a typical power plant, therefore "hot side" precipitators which operate with gas temperature higher than the condensation point for most POM's fail to collect considerable amounts of BaP (*30*). Fabric filters are efficient collectors of fine particles but may become

blocked by tarry particles or, if operated at high temperature, may fail to trap vapor BaP (*30*).

Stationary source control of BaP entails use of technologies that can effectively condense or collect BaP vapor (e.g., high energy scrubbers) as well as devices that can maximize capture of fine particulates. According to OTA (*21*), fine particulate controls alone will probably reduce BaP emissions by 85-90%.

For intermediate-size boilers, cyclones and ESP's are the most commonly used; yet for reasons just mentioned they are not adequate BaP control methods. As for residential furnaces, many such boilers have little or no particulate control of any kind (*30*).

In addition to improved technologies that control emission of BaP vapor and fine particulate material, adjustments in the type of fuel, change in combustion process, and use of afterburners can be used to reduce BaP (*4, 27*). In some cases (as in coke oven operations), hydrocarbons may be recovered from effluent streams and recycled (*130*).

BaP control methods suggested for stationary diesel engines include water scrubbers and spiral filter beds (*178*). BaP controls for diesel-powered automobile emissions are presently evolving. The major methods being considered are the trap oxidizer (catalytic and noncatalytic), and engine modifications; while afterburners and fuel modification are also being explored (*179*).

The effectiveness of technologies to control BaP and related emissions from synfuels processing and combustion plants is so far unknown. High temperature and high pressure particulate control equipment is being studied but is unlikely to collect BaP efficiently for reasons cited earlier (*30*).

Another approach to BaP control is to substitute less polluting energy sources such as natural gas, solar energy, etc., for conventional sources of energy. A third solution—in addition to control technologies and alternative sources of energy—is conservation. According to Stobaugh and associates at the Harvard Business School (*180*): "If the U.S. were to make a serious commitment to conservation, it might well consume 30-40% less energy . . . and still enjoy the same or higher standard of living. This would require only modest adjustments in the way people live." (p. 136)

Absence of Standards for BaP

At this time there are no health or environmental standards for BaP or for fine particulate matter in the U.S. (*130*). Therefore, there is little incentive for industry to take steps to control emissions of these pollutants. The only relevant standard is the occupational standard for coke oven emissions (CFR) (*181*). EPA does not anticipate proposing standards specific for BaP (*182*).

The absence of BaP standards in the U.S. is all the more striking in view of the standards adopted in 1972 and 1973 for the U.S.S.R. consisting of a maximum exposure level of 1 ng/m^3 in ambient air and a maximum allowable concentration (MAC) of 150 ng/m^3 in work environments (*183*). Shabad (*183*) stresses the fact that the Ministry of Health of the U.S.S.R. does not consider the MAC to be a safe level but rather to be the "maximum unavoidable dose." Table 2 shows that U.S. ambient BaP concentrations have significantly exceeded the U.S.S.R. maximum exposure level.

Specifically reviewing the potential human health impacts of coal combustion, the OTA (*21*) urges EPA to carry out the provision of the Clean Air Act Amendments of 1977 that the Agency study the health effects of fine particles, associated trace elements, and POM to establish regulatory controls if necessary. Existing data reviewed above indicate that BaP is a candidate for regulation under the Clean Air Act (*184*). The Clean Air Act provides several means of regulating BaP: through a nationwide ambient air quality health standard under Sections 108 or 109; through standards of performance for new and existing sources of BaP (Section 111); or through emissions standards for hazardous air pollutants under Section 112. Sections 108, 109, and 111 address pollutants which may "reasonably be expected to endanger public health," while Section 112 requires EPA to list as a hazardous air pollutant each substance that "may reasonably be anticipated to result in an increase in mortality or an increase in serious, irreversible, or incapacitating reversible illness." One or possibly a combination of these regulatory approaches is necessary to protect public health from airborne BaP.

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